For debate

Hepatitis C: universal or selective screening?

R P Brettle

The major aim in screening for any disorder is the prevention of future ill health and/or the treatment of asymptomatic clinical disease. Guidelines have been produced with regard to physician initiated screening for medical conditions; most importantly, the condition should be an important health problem, there should be an accepted form of treatment, a suitable and acceptable test, and facilities for its diagnosis; the natural history should be well understood and a latent or early symptomatic phase is necessary to allow time for any possible intervention.[1] At first glance these guidelines appear to be admirably fulfilled for infection with hepatitis C virus (HCV) and, without much discussion, widespread screening for this disorder has been initiated particularly among those infected via injecting drug use (IDU).

Without a doubt HCV is an important health problem; 80% of those infected develop chronic liver disease and it is a major cause of chronic liver disease which in the United States is only slightly less common than that caused by chronic alcoholism.[2 3] In the United Kingdom around 3000 blood donors have been confirmed as HCV antibody positive, around 5000 haemophiliacs are estimated to have been infected before screening for HCV was introduced, and around 100 000 individuals are estimated to have been infected via IDU.[4]

There is an acceptable treatment, interferon alfa, and relatively simple blood tests for the diagnosis or monitoring of treatment for HCV infection, although a more invasive procedure in the form of a liver biopsy may also be required.[3] There is a very definite latent or early symptomatic phase with a possible median time to serious disease (cirrhosis) of maybe 30 years or longer.[5] Despite these apparent advantages for screening there are some technical problems, particularly that some patients may be missed by current tests. We now know that loss of HCV antibody occurs at a rate of around 0.6/100 patient years but that this does not necessarily imply loss of virus or infectivity.[2] Thus, for every 1000 infected patients screened six will have a negative test after 1 year of HCV infection, 60 after 10 years, 120 after 20 years, and 180 after 30 years of infection, an error rate of around 1–2%. For individuals with a definite risk activity, like IDU, this can be overcome by testing earlier specimens or arranging for a PCR test if early specimens are not available. Thus, as always if undertaking screening, it is important to be aware of the implications and limitations of a negative test as much as a positive test.

Unlike HIV, there has been no major debate on the wisdom or not of widespread screening for HCV in at risk populations. In 1995 under the aegis of the Royal College of Physicians Edinburgh, the medical director of the Scottish Blood Transfusion Service met with a group of interested clinicians to discuss the problem of screening for individuals possibly infected with HCV via blood transfusions.[6] Their conclusion concerning anyone possibly at risk of HCV from a blood product was:

"Person identified as being potentially HCV positive must be told . . . there is a duty to provide care and support for these patients to the highest clinical standards."

Was this conclusion reasonable, can it be applied to all other individuals at risk of HCV infection, or was it simply related to the possibility of legal action? Since it may take 30 years to develop clinical disease or illness from HCV who is the beneficiary from widespread screening for HCV—the patient or the community? Are we trying to prevent spread of HCV infection, reduce progression to disease, or reduce legal liability? In the case of HIV, which is readily transmissible via both IDU and sexual intercourse and is a major threat to the non-drug using population, considerable efforts were made to set up counselling services and treatment facilities. By comparison, screening for HCV, which is rapidly spread via injecting drug practices but rather inefficiently spread via sexual intercourse, has received little attention and little in the way of additional resources.

The only therapy of proved benefit for chronic HCV hepatitis is interferon alfa, which is effective in only around 20% of patients and unfortunately has a number of exclusions and difficult side effects.[3] In Edinburgh, where additional funds for the treatment of HCV have not been allocated, individuals are not eligible for shared care interferon therapy with general practitioners if the treatment is likely to be ineffective or if there is an increased risk of an adverse event. Individuals currently excluded from the shared care protocol are those with the following problems—obesity (a body mass index >35); an immunocompromised state; in the presence of liver failure or early cirrhosis, pre-existing hepatocellular carcinoma; other causes for chronic liver disease such as alcohol, autoimmune hepatitis, significant comorbidity such as cardiac or renal disease; poor compliance with injection therapy or follow up; specific contraindications to interferon therapy such as depression, epilepsy, psoriasis, poor central neurological function; and of course any previous allergy to interferon. If these exclusion criteria for treatment are to be applied, is it then ethical to screen an individual at risk for HCV in the presence of a pre-existing exclusion criterion for treatment? Similarly, if the facilities for diagnosis and treatment of HCV were not available, either as a result of a lack of expertise or lack of funds

Regional Infectious Disease Unit (RIDU), City Hospital, Edinburgh EH10 5SB
R P Brettle

Accepted for publication
4 August 1998

then again it would seem unreasonable to actively screen individuals for HCV until such funds were made available. The danger, of course, is that a health authority by failing to provide funds for diagnosis would effectively remove the requirement to fund treatment. However, it certainly behoves doctors to ask themselves if it is reasonable to initiate screening of patients at risk of HCV if there is no possibility of any form of treatment either because of an exclusion criterion, lack of response, an adverse event, or simply a lack of available funds.

Since HCV has a natural history that may stretch to three decades, are there constraints, other than specific exclusion criteria for treatment or lack of funds, that we should consider before screening for HCV? Is it necessary for instance to consider comorbidity factors with an increased risk of ill health or death? Should the risk of morbidity and mortality from conditions such as a drug overdose, smoking, or alcohol consumption be taken in to consideration in decisions to screen for HCV and offer treatment for HCV. If the risks from IDU associated comorbidity exceed those for HCV is it reasonable to proceed to HCV screening or treatment? In the presence of excessive alcohol the rate of progression to cirrhosis is increased by 25%. Would it be reasonable to deny treatment for HCV until this important cofactor has been removed? Studies of drug users suggest a 1% risk of death/year (mainly from drug overdoses). If this estimate is correct then over 30 years the overdose death rate would be of the order of 25% compared with a 50% chance of cirrhosis and an unknown death rate. It is important to remember however that for 31% of infected individuals no progression to cirrhosis would occur for up to 50 years while for 33% progression would have occurred before 20 years had passed.[5] In addition, in the context of post-transfusion HCV there was no overall increase in mortality after 18 years although the mortality from liver disease was 3.3% compared with 1.5% in controls.[5]

While such factors may be important at present these sorts of guidelines for screening or limitations on access for treatment are not being applied to other individuals exposed to HCV (or any other condition for that matter) so why should such decisions be applied to those infected via IDU? Equally, what was the harm reduction programme for IDU supposed to achieve? Its primary aim was to prevent early death and morbidity from IDU. Having achieved that objective is it then reasonable to allow an individual to suffer from HCV having evaded HIV?

To date, there has been no investment in counselling services for the very large numbers of individuals infected via IDU and there has been very little thought given to the emotional problems that result from widespread screening for HCV. This was a particularly emotive problem for HIV and it is only now, with the advent of highly active antiretroviral therapy, that widespread screening for HIV is being accepted as advantageous.

An important alternative to a broad based screening approach currently being applied to HCV would be selective screening based on identifying individuals at greatest risk for HCV progression or those with most to gain from early treatment. Since the risk of serious liver damage increases with age at infection and the length of infection with HCV these factors would provide a logical method of identifying those at greatest risk; a current or ex-IDU of 10 years' standing who started perhaps in his 40s or 50s would be at increased risk of cirrhosis compared with a 21–30 year old with only a 2–3 year history of IDU. Recent estimates of time to cirrhosis ranged from 38 years for infection between 21–30 years of age to only 12 years for those over 50 year of age at the time of infection. Since it appears that 80% of IDU are infected within the first year of injecting and sharing of drugs, length of drug use would be another logical means of targeting those at greatest risk from HCV. More than 50 g of alcohol per day increases the rate of fibrosis by around 33%; screening with informed consent of at risk individuals with a high alcohol intake would also be logical. After all the subsequent information might allow for a change in behaviour that would alter the risks of progression. Lastly, even though the risk is low, screening in an attempt to provide informed consent for pregnancy or the protection of sexual partners, would also be logical.

It therefore seem reasonable to judge the decision to screen for HCV to be made on the likely benefits for the individual rather than on whether or not an individual is a drug user or even on any possible benefits for society. Essentially, a policy of targeted screening based on increased risk either for the individual or society seems the best way forward until the gains from therapy are substantial.

1 Calman K. Developing screening in the NHS. *Journal of Medical Screening* 1994;**1**:101–5.
2 Alter MJ, Margolis HS, Krawcznski K, *et al*. The natural history of community acquired hepatitis C in the United States. *N Engl J Med* 1992;**327**:1899–905.
3 Hoofnagle JH, Di Bisceglie AM. The treatment of chronic viral hepatitis. *N Engl J Med* 1997;**336**:347–56.
4 McMenamin J. Hepatitis C virus: prevalence and treatment. *ANSWER* 1994;AM-5 WR 94/47:3–4. Glasgow: Scottish Centre for Infection and Environmental Health, 1994.
5 Poynard T, Bedossa P, Opolon P, for the OBSVIRC, CLINIVIR and DORSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;**349**:825–32.
6 Royal College of Physicians of Edinburgh. Hepatitis C in the context of Blood Transfusion Service. Lookback studies and similar circumstances in Scotland. A report produced by a working party. Edinburgh: RCPE, 1995.